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Frequency and determinants of mild cognitive impairment among diabetic type II patients attending a secondary care hospital in Makkah, Saudi Arabia

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Abstract
Aim: Type II diabetes mellitus (TIIDM) is a common metabolic disorder, recent substantial amount of evidence showed that TIIDM is a risk factor for mild cognitive impairment (MCI). MCI can impede the management of patients, which can lead to increased risks of complications, functional disability and healthcare costs. The aim of this study is to measure the frequency and determinants of MCI among diabetic type II patients (TIIDM) attending the Diabetic Center at Al-Noor specialist hospital (NSH) in Makkah, Saudi Arabia.
Material and Methods: For this cross-sectional study, 179 TIIDM patients were recruited. A self-constructed validated questionnaire was used for data collection. The Arabic validated version of the Montreal Cognitive Assessment- Basic (MoCA-B) was used to diagnose MCI.
Results: Participants were equally distributed according to gender. Ages ranged from 31 to 80 years (58.6±9.6 years). The prevalence of MCI was 66.5% with 95% CI (0.6-0.7). MCI was found significantly higher in the elderly (p=0.046), in those who never practiced physical exercise (p<0.001), who had uncontrolled diabetes (p<0.001), cataract (p=0.001), diabetic retinopathy (p=0.003). Multivariate analysis showed that older patients were more likely to develop MCI (adjusted odds ratio "AOR"=1.3; 95% CI: 1.0-1.7), patients who never practiced physical exercise were more likely to develop MCI (AOR=5.4; 95% CI: 2.4-12.1), patients with cataract were at twice risk to develop MCI (AOR=2.3; 95%CI: 1.0-5.3), as well as patients with diabetic retinopathy (AOR=2.7; 95%CI: 1.4-5.3). Patients with uncontrolled diabetes had also an 11-fold higher risk of MCI (AOR=11.9; 95%CI: 5.1-27.7). Patients with hypertension were nine times more likely to develop MCI (AOR=9.3; 95%CI: 4.2-23.3). Patients with dyslipidemia had twice the risk (AOR=2.4; 95%CI: 1.2-4.8).
Discussion: Mild cognitive impairment is prevalent among TIIDM patients attending the Diabetic Center at NSH, Makkah. Elderly patients, patients who had never practiced physical exercise, complicated by cataract and diabetic retinopathy, those with uncontrolled diabetes, and patients with co-morbid hypertension and dyslipidemia were at a higher risk for developing MCI.

Keywords
Diabetes mellitus; Mild cognitive impairment; MoCA

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Introduction

Diabetes mellitus (DM) is a significant global health burden worldwide, in 2017 there were 451 million people with diabetes, and this number is expected to increase to 693 million by 2045 [1].

Saudi Arabia has the highest prevalence of DM in the Middle East and South Africa region (MENA), ranging between 18.2–31%, with 24% of the health care budget spent on DM [2]. Complications of DM are well-known and studied. However, the impact of DM on neurocognitive functions is not well addressed, and the pathophysiology has not been understood. A large body of substantial evidence showed that the prevalence of MCI among patients with DM was higher compared to control groups of patients without DM [3]. This is an exceptionally high in TIIDM patients [4]. Previous studies suggest that TIIDM patients have an estimated 50% risk of developing dementia. Therefore, TIIDM is not only a risk factor for MCI, but also promotes the transformation of MCI into dementia [5]. Mild cognitive impairment is a transitional state between normal cognition and the development of dementia, with the preservation of daily life activity independency [6]. There are many proposed mechanisms in which TIIDM can affect cognition:

1) DM is a significant risk factor for stroke, and TIIDM is frequently associated with metabolic syndrome (dyslipidemia, hypertension, obesity and insulin resistance), which are also risk factors for the development of dementia [5].

2) Chronic hyperglycemia leads to the binding of sugars with different proteins and forms advanced glycation end products that leads to inflammatory cascade, which causes direct damage to the brain tissue and blood vessels, causing micro-infarcts and generalized atrophy [7].

3) In the early stages of TIIDM, the insulin level is high to compensate for insulin resistance; this stimulates the secretion of amyloid- beta to the extracellular matrix, inhibiting its degradation and formulating senile plaques [8]. As life expectancy improves in Saudi Arabia, the number of elderly over 65years of age is expected to grow from 72 to around 80 years, and this age group will continue to grow, so it is extremely important to understand the changes that happen to cognition, especially in pathological changes that happen in DM [9]. Furthermore, cognitive deficit may occur at the earliest stages of diabetes and is further exacerbated by metabolic syndrome, thus diabetes in early mid-life is associated with 19% cognitive impairment over 20 years [10]. In Saudi Arabia, studies evaluating the prevalence of MCI in T2DM in the Arabic region are scarce. Only one study was found in Jeddah with 17.1% prevalence [11]. The study included only middle-aged and elderly patients, while the current study included younger patients as well. In addition, the current study investigated the relationship between MCI and complications of diabetes. Tools used for MCI screening in a previous study were initially validated in a sample of individuals with a high level (≥ 13 years) of formal education. As a result, there is a chance for bias when illiterate older adults or those with low levels of education are screened for MCI [12]. Therefore, the current study used the (MoCA-B) to test participants who are illiterate or have a low level of education (less than five years) [13]. In the absence of treatment for dementia, mild cognitive impairment has become an essential target for early diagnosis and treatment to slow the disease progression and to modify risk factors to result in significant benefit for both the patient and the caregiver. Therefore, this study aimed to estimate the frequency of MCI among TIIDM patients and identify the relationship between diabetes-related characteristics and MCI.

Material and Methods

This analytical cross-sectional study was conducted at the diabetic center in NSH, Makkah, Saudi Arabia in September 2019.

A total of 179 patients with TIIDM were recruited, the criteria for diagnosing TIIDM according to the American Academy of Diabetes (ADA) are either one of the following: 1- Fasting blood glucose ≥ 126mg/dl; 2- Glycated hemoglobin (HbA1c) ≥ 6.5%; 3- Two-hour plasma glucose ≥ 200mg/dl during an oral glucose tolerance test with a glucose load of 75g; 4- Random blood glucose ≥ 200mg/dl with symptoms of hyperglycemia or hyperglycemic crisis [14]. The exclusion criteria were as follows: stroke, Alzheimer's disease, head injury, psychiatric disorders, depression, alcohol dependence, drug dependence, and use of antidepressant or antipsychotic medications. The researcher followed a systematic random technique to choose the study participants, the number of patients seen in September was determined and divided by 22 (number of working days). Participants were selected using a random number generator.

Participants were invited to participate and sign written informed consent, and then interviewed in a private room to ensure privacy. The researcher was officially trained and certified to use the Arabic version of MoCA-B and to collect the following data: socio-demographic, level of exercise according to the ADA guidelines ≥150 min/week, hypertension and dyslipidemia, both on medications or according to the Eighth Joint National Committee and Dyslipidemia Adult Treatment Panel IV, respectively, diabetes-related characteristics (type of treatment, compliance on medications, recent glycated hemoglobin), diabetes complications, body mass index and smoking status.

Saleh et al. translated the MoCA-B from English to Arabic version in 2017 with Cronbach's alpha on the standardized items of (0.91) with 98% sensitivity and 93% specificity as a screening tool for MCI, particularly in elderly and low-educated patients [13].

MoCA-B assesses the following cognitive domains in each patient: 1- Executive functions (1 point); 2- Immediate recall (No points); 3- Language fluency (2 points); 4- Orientation (6 points); 5- Calculation (3 points); 6- Abstraction (3 points); 7- Delayed recall (5 points). 8- Visual perception (3 points); 9- Naming (4 points); 10- Attention (3 points). The time to administer the MoCA-B is approximately 15 minutes. The maximum score is 30 points (a score of <24 is considered mild cognitive impairment), to correct residual education bias or literacy, 1 point is added to the total score of subjects with less than four years of education or if the subject is illiterate (defined as the inability to read or write fluently in daily living) [12].

The statistical program for social sciences (SPSS), version 25 was used. Categorical variables were presented as frequency and percentage, whereas continuous variables were presented

as means ± standard deviation (SD). The median (interquartile range "IQR" for abnormally distributed variables) was also computed. Variables were compared using the Student t-test, Mann-Whitney test, Chi-square test and Fischer's exact test (bivariate analysis). Multivariate logistic regression analysis was applied to control the effect of confounding where the significant variables from the bivariate analysis were included in the model. P–value < 0.05 was considered as statistically significant.

Approval for the study was obtained from the Institutional Review Board of the Ministry of Health. All the information of the patient was kept confidential and used only for research purposes.

Results

The study included 179 TIIDM patients. They were almost equally distributed according to gender. Their age ranged from 31 to 80 years (58.6±9.6 years). The majority of them were married (84.3%). Regarding their educational level, 28.6% were Bachelor holders, whereas 21.2% were illiterates.

The majority of TIIDM patients were either overweight (39.1%) or obese (49.2%); 12.8% practiced physical exercise. One-fifth of the participants (21.8%) were smokers.

Regarding co-morbid chronic diseases, the commonest reported were hypertension (79.9%) and dyslipidemia (70.9%), only (18.4%) had ischemic heart disease and (19.6%) had chronic kidney disease.

The most frequent reported diabetic complications were retinopathy (70.9%), peripheral neuropathy (68.7%), diabetic foot ulcer (47.5%) and cataract (41.9%), the least reported diabetic complications were renal insufficiency (16.8), heart failure (14.5%), glaucoma (10.6%), myocardial infarction (9.5%) and limb amputation (3.9%).

A history of the previous hospitalization because of hyperglycemia was reported by 24.6%. Glycemic control based on (HbA1c%) was uncontrolled in 70.4% of the participants.

The prevalence of MCI among TIIDM patients attending diabetic center at NSH in Makkah, 2019 was 66.5% with 95% CI (0.6-0.7).

Factors associated with MCI

The age of TIIDM patients with MCI was significantly higher than that of those without MCI (60±9.8 versus 56±8.9 years), p=0.046. The highest rate of MCI was reported among illiterate patients (89.5%), whereas the lowest rate was observed among bachelor's degree holders (52.9%), p=0.007.

MCI was more significantly reported among patients who never practiced physical exercise than those practicing physical exercise (80.2% versus 46.6%), p<0.001. The highest MCI was reported among patients with duration of diabetes ≥17 years (85.7%), p=0.029. Patients with a history of previous hospitalization because of hyperglycemia were more likely to have MCI compared to those without such a history (79.5% versus 62.2%), p=0.035. Patients with uncontrolled blood glucose were more likely to develop MCI than those with controlled levels (81.7% versus 30.2%), p<0.001 (Table 1).

Patients who had cataract were more likely to develop MCI than those who did not (80% versus 56.7%), p=0.001. Similarly, those with diabetic retinopathy were more likely than their

Table 1. Association between diabetes-related characteristics among patients and MCI

	Mild cognitive impairment		p-value*
	Present N=119 N (%)	Absent N=119 N (%)	
Practicing physical exercise			
Yes (n=73)	34 (46.6)	39 (53.4)	<0.001*
No (n=106)	85 (80.2)	21 (19.8)	
Duration of diabetes (years)			
<5 (n=23)	13 (56.5)	10 (43.5)	0.029*
5-10 (n=46)	29 (63.0)	17 (37.0)	
11-16 (n=75)	47 (62.7)	28 (37.3)	
≥17 (n=35)	30 (85.7)	5 (14.3)	
History of previous hospitalization because of hyperglycemia			
Yes (n=44)	35 (79.5)	9 (20.5)	0.035*
No (n=135)	84 (62.2)	51 (37.8)	
Glycemic control based on glycated hemoglobin level (HbA1c%)			
Controlled (n=53)	16 (30.2)	37 (69.8)	<0.001*
Uncontrolled (n=126)	103 (81.7)	23 (18.3)	

*Chi-square test

Table 2. Association between diabetic complications, co-morbidities among type II diabetic patients and mild cognitive impairment

	Mild cognitive impairment		p-value*
	Present N=119 N (%)	Absent N=60 N (%)	
Diabetic foot ulcer			
Yes (n=75)	61 (81.3)	24 (32.0)	0.154*
No (n=94)	58 (61.7)	36 (38.3)	
Limb amputation			
Yes (n=7)	7 (100)	0 (0.0)	0.054**
No (n=172)	112 (65.1)	60 (34.9)	
Renal insufficiency			
Yes (n=35)	25 (71.4)	10 (28.6)	0.383*
No (n=144)	94 (65.2)	50 (34.7)	
Peripheral neuropathy			
Yes (n=123)	79 (64.2)	44 (35.8)	0.344*
No (n=56)	40 (71.4)	16 (28.6)	
Glaucoma			
Yes (n=19)	16 (84.2)	3 (15.8)	0.065**
No (n=160)	103 (64.4)	57 (35.6)	
Cataract			
Yes (n=75)	60 (80.0)	15 (20.0)	0.001*
No (n=104)	59 (56.7)	45 (43.3)	
Diabetic retinopathy			
Yes (n=127)	93 (73.2)	34 (26.8)	0.003*
No (n=52)	26 (50.0)	26 (50.0)	
Ischemic heart diseases			
Yes (n=89)	57 (64.0)	32 (36.0)	0.492*
No (n=90)	62 (68.9)	28 (31.1)	
Hypertension			
Yes (n= 143)	110 (76.9)	33 (23.0)	<0.00*
No (n=36)	9 (25.0)	27 (75.0)	
Dyslipidemia			
Yes (n=127)	92 (72.4)	35 (27.5)	0.007*
No (n=52)	27 (51.9)	25 (48.0)	

* Chi-square test ** Fischer exact test

Table 3. Predictors of mild cognitive impairment among type II diabetic patients: Multivariate logistic regression analysis

	AOR	95% CI	p-value
Age			
56	1.0	---	---
60 ®	1.3	1.0-1.7	0.048
Practicing physical exercise			
Yes	1.0	---	---
Never ®	5.4	2.4-12.1	<0.001
History of cataract			
Yes ®	1.0	---	---
No	2.3	1.0-5.3	0.046
History of diabetic retinopathy			
Yes ®	1.0	---	---
No	2.7	1.4-5.3	0.003
Glycemic control			
Controlled	1.0	---	---
Uncontrolled ®	11.9	5.1-27.7	<0.001
Hypertension			
Yes ®	1.0	---	---
No	9.3	4.2-23.3	<0.001
Dyslipidemia			
Yes ®	1.0	---	---
No	2.4	1.2-4.8	0.009

AOR: Adjusted odds ratio CI: Confidence interval
® Reference category
Terms of educational level, duration of diabetes, previous history of hospitalization due to hyperglycemia were removed from the final model (not significant)

counterparts to have MCI (73.2% versus 50%), p=0.003. Other diabetic complications were not significantly associated with the prevalence of MCI. Patients with hypertension are more likely to have MCI compared to those without hypertension (76.9% versus 25.0%), p<0.05, also patients with dyslipidemia were significantly higher for MCI compared to patients without dyslipidemia (72.4% versus 51.9%), p=0.007 (Table 2).

Multivariate logistic regression analysis

Table 3 shows that older patients are more likely to develop MCI than others (adjusted odds ratio "AOR"=1.3; 95% confidence interval "CI": 1.0-1.7), p=0.048. Patients who never practiced physical exercise were more likely to develop MCI than those practicing physical exercise (AOR=5.4; CI: 2.4-12.1), p<0.001. Diabetic patients complicated by cataract were at almost double risk to develop MCI compared to those without cataract (AOR=2.3; 95%CI: 1.0-5.3), p=0.046, similar to this finding observed as well in patients with diabetic retinopathy (AOR=2.7; CI: 1.4-5.3), p=0.003. Patients with uncontrolled diabetes were at an 11-fold risk of MCI compared to those with controlled diabetes (AOR=11.9; 95% CI: 5.1-27.7), p<0.001. Patients with hypertension were nine times more likely to develop MCI than those without high blood pressure (AOR=9.3; 95%CI: 4.2-23.3), p<0.001. Patients with dyslipidemia were at a double risk of developing MCI compared to those without dyslipidemia (AOR=2.4; 95%CI: 1.2-4.8), p=0.009. Patients` educational level, duration of diabetes, and previous history of hospitalization due to hyperglycemia were not significantly associated with MCI.

Discussion

The prevalence of MCI among diabetic TIIDM patients in the present study was 66.5%. This is higher than in those reported in other recent studies carried out in Saudi Arabia, Jeddah 17.1% [11]. Even lower rate has been observed in a study carried out in China 13.5% [15]. The observed variation in the prevalence rates between studies could be due to using different tools for diagnosis and/or different cut-offs or difference in the characteristics of the study populations. A higher rate of MCI among diabetic patients is expected as a meta-analysis study showed a 20% pooled increased risk of MCI among diabetic patients compared to healthy people [3]. In the multivariate logistic regression analysis of the current study, the age of type II diabetic patients with MCI was significantly higher than that of those without MCI. This is in accordance with multiple studies that showed that elderly with TIIDM are at a higher risk for mild cognitive impairment and dementia [15,16]. As people age, the human brain undergoes different structural and functional changes, including neuron loss, decreased synaptic density and signaling, which lead to a decline in cognitive functions, added to that, as patients with TIIDM age, the brain gets atrophied and lacunar infarcts happen, which accelerates the cognition decline [17]. However, Rawlings et al. found that cognitive impairment in TIIDM patients can occur at all ages [10]. Attention should be drawn to the prevention and control of mild cognitive impairment in middle age type II diabetic patients.

In a study carried out in Romania Oana Albai, BMI was significantly higher in diabetic patients with MCI [18]. Yanbo Li and his colleagues also concluded that a high waist circumference increased the risk of cognitive impairment, rather than a high body mass index [19]. In accordance with another study, MCI in the current study was more significant among patients who never practiced physical exercise compared to those practicing physical exercise, and this effect remained after control for the confounding effect [20]. This finding enforces the role of practicing physical exercise among diabetic patients to improve cognitive functions.

The mechanism of the association between diabetes mellitus and cognitive impairment is unclear. However, some possible mechanisms have been mentioned. Some believe that hyperglycemia is responsible for abnormalities in cognitive impairment in patients with type II diabetes mellitus. Dik et al. reported that hyperglycemia has the strongest relation to the risk of cognitive impairment [21]. In agreement with that, in our study we found that patients with a history of previous hospitalization because of hyperglycemia were more likely to have MCI.

In accordance with other studies, in the present study, even after control for confounders, patients with uncontrolled diabetes defined by high concentration of (HbA1C) were at a higher significant risk of MCI compared to those with controlled diabetes. Zilliox et al. reported that poor glycemic control increased the risk of developing cognitive impairment in TIIDM patients [4]. Hyperglycemia disrupts the blood- brain barrier and causes an influx of inflammatory markers that directly damage neuron cells, decrease synaptic signaling, reduce the brain blood flow, and accelerate the rate of MCI development [22]. In a study carried in Romania, obesity, hypertension, and dyslipidemia were associated with the prevalence of MCI among type II diabetic patients [18]. It has been documented that

hypertension produces vascular dysfunction that compromises blood and glucose supply to the brain and decreases the clearance of substances causing oxidative stress and eventually neuronal degeneration [23]. In the present study, triglyceride levels were significantly higher among patients with MCI than among those without MCI. This could be explained by the ability of triglycerides to cross the blood–brain barrier rapidly, by their presence in the cerebrospinal fluid, induce central leptin and insulin receptor resistance, which consequently lead to decreasing cognition [24]. Several systematic reviews explored the association between diabetic retinopathy (DR) and MCI, and these studies found that diabetic retinopathy doubles the risk of developing MCI. In accordance with these studies, the current study found that patients with DR were twice as likely to be at risk for MCI. TIIDM patients can develop both conditions with DR earlier than MCI, as the optic nerve is more sensitive to hyperglycemia [25].

This study explored an important problem among TIIDM patients and identified some associated factors that could help in the organization of preventive programs. Primary healthcare physicians and diabetologists should play a more active role in prevention. Early identification and treatment of MCI among TIIDM patients and measures to control blood glucose among patients with DM are urgently needed. Further larger multi-center longitudinal studies investigating MCI among diabetic patients in Makkah are needed.

Conclusion

Mild cognitive impairment is prevalent among TIIDM patients attending the Diabetic Center at NSH, Makkah. Older patients, patients who never practiced physical exercise, complicated by cataract and diabetic retinopathy, those with uncontrolled diabetes and patients with co-morbid hypertension and dyslipidemia were at a higher risk for developing MCI.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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